

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NEREUS.109VP	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/043668	International filing date (day/month/year) 02/12/2005	(Earliest) Priority Date (day/month/year) 03/12/2004
Applicant NEREUS PHARMACEUTICALS, INC.		
<p>This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.</p> <p>This international search report consists of a total of <u>5</u> sheets.</p> <p><input checked="" type="checkbox"/> It is also accompanied by a copy of each prior art document cited in this report.</p>		
<p>1. Basis of the report</p> <p>a. With regard to the language, the international search was carried out on the basis of:</p> <p><input checked="" type="checkbox"/> the international application in the language in which it was filed <input type="checkbox"/> a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))</p> <p>b. <input type="checkbox"/> With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.</p> <p>2. <input checked="" type="checkbox"/> Certain claims were found unsearchable (See Box No. II)</p> <p>3. <input type="checkbox"/> Unity of invention is lacking (see Box No III)</p> <p>4. With regard to the title,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant <input type="checkbox"/> the text has been established by this Authority to read as follows:</p> <p>5. With regard to the abstract,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant <input type="checkbox"/> the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority</p> <p>6. With regard to the drawings,</p> <p>a. the figure of the drawings to be published with the abstract is Figure No. <u>10E</u> <input checked="" type="checkbox"/> as suggested by the applicant <input type="checkbox"/> as selected by this Authority, because the applicant failed to suggest a figure <input type="checkbox"/> as selected by this Authority, because this figure better characterizes the invention</p> <p>b. <input type="checkbox"/> none of the figures is to be published with the abstract</p>		

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/043668A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/397 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/138196 A1 (FENICAL WILLIAM ET AL) 15 July 2004 (2004-07-15) page 4, left-hand column, paragraph 2 – right-hand column, paragraph 1 page 3, right-hand column, paragraph 2-4 page 4, right-hand column, paragraph 4 – page 5, left-hand column, paragraph 1 ----- -/-	12-30
Y		1-37

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search 11 April 2006	Date of mailing of the international search report 12/05/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Young, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/043668

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FELING ROBERT H ET AL: "Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus <i>salinospora</i> " ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, WILEY VCH VERLAG, WEINHEIM, DE, vol. 42, no. 3, 20 January 2003 (2003-01-20), pages 355-357, XP002304842 ISSN: 1433-7851 page 356, right-hand column, paragraph 3	1-37
Y	ELLIOTT P J ET AL: "The proteasome: A new target for novel drug therapies" AMERICAN JOURNAL OF CLINICAL PATHOLOGY, PHILADELPHIA, PA, US, vol. 116, no. 5, November 2001 (2001-11), pages 637-646, XP008007324 ISSN: 0002-9173 the whole document	1-37
P,X	WO 2005/002572 A (NEREUS PHARMACEUTICALS, INC; PALLADINO, MICHAEL; NEUTEBOOM, SASKIA, TH) 13 January 2005 (2005-01-13) page 64, lines 4-6 examples 18,20,34,41,42 claims 1-24	1-37
P,X	WILLIAMS PHILIP G ET AL: "New cytotoxic salinosporamides from the marine actinomycete <i>Salinispora tropica</i> " JOURNAL OF ORGANIC CHEMISTRY, vol. 70, no. 16, August 2005 (2005-08), pages 6196-6203, XP002376431 ISSN: 0022-3263 page 6197, left-hand column, paragraph 1	1-37
P,X	MACHERLA VENKAT R ET AL: "Structure-activity relationship studies of salinosporamide a (NPI-0052), a novel marine derived proteasome inhibitor" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 11, June 2005 (2005-06), pages 3684-3687, XP002376432 ISSN: 0022-2623 page 3684, left-hand column	1-37

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International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1–24 and 31–37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/043668

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 2004138196	A1	15-07-2004	US 2004259856	A1 23-12-2004
WO 2005002572	A	13-01-2005	AU 2004253478	A1 13-01-2005
			CA 2532066	A1 13-01-2005
			EP 1638552	A2 29-03-2006

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2005/043668

International filing date (day/month/year)
02.12.2005

Priority date (day/month/year)
03.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/397 A61P35/00

Applicant
NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Young, A

Telephone No. +49 89 2399-7811



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 the international application in the language in which it was filed
 a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 on paper
 in electronic form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in electronic form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- the entire international application
- claims Nos. 1-24 and 31-37

because:

- the said international application, or the said claims Nos. with respect to Industrial Applicability relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- no international search report has been established for the whole application or for said claims Nos.
- a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See Supplemental Box for further details

**WRITTEN OPINION OF THE
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International application No.
PCT/US2005/043668

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-11, 31-37
	No: Claims	12-30
Inventive step (IS)	Yes: Claims	1-11, 37
	No: Claims	12-36
Industrial applicability (IA)	Yes: Claims	25-30
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
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Re Item III:

1. Claims 1-24 and 31-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V:

2. The documents considered in the present processing are consecutively numbered D1-D6; this numbering results from the citations D1-D6 found in the International Search Report (ISR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.
3. The application refers to a method of treating a neoplastic disease with a compound of formula (I), preferably salinosporamide A, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent. Further, a method of treating a neoplastic disease with a compound of formula (I) in combination with at least one additional chemotherapeutic agent and a pharmaceutical composition comprising a compound of formula (I) in combination with at least one additional chemotherapeutic agent is claimed. Finally, a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors is claimed.
4. Novelty, Article 33(2) PCT
 - 4.1 The subject-matter of claims 12-30 is considered to lack novelty over the disclosure of D1 within the meaning of Article 33(2) PCT for the following reasons:

D1 discloses salinosporamide A, which is encompassed by formula (I), for the treatment of neoplastic diseases, e.g. non-small-cell lung cancer or prostate cancer. Also the combination chemotherapy of salinosporamide compounds with other neoplastic agents, e.g. doxorubicin, tamoxifen is disclosed.
 - 4.2. The subject-matter of claims 1-11 and 31-37 is novel over the cited prior art within the meaning of Article 33(2) PCT.

**WRITTEN OPINION OF THE
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None of the cited references discloses a method of treating a neoplastic disease with a compound of formula (I), preferably salinosporamide A, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent.

Also a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors is not found in the cited prior art.

5. Inventive step, Article 33(3) PCT

5.1 The object underlying the present application is the provision of a method of treating a neoplastic disease, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent.

The posed solution is the use of a compound of formula (I), preferably salinosporamide A.

The use of salinosporamide A for the treatment of neoplastic diseases is known from the cited prior art.

Document D2 discloses the in vitro cytotoxicity of salinosporamide A in different cancer cell lines.

However, the use for a salinosporamide for the treatment of a neoplastic disease, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent is not known and also not suggested in the cited prior art.

Thus, an inventive step can be acknowledged for the subject-matter of claims 1-11 within the meaning of Article 33(3) PCT.

5.2 The subject-matter of claims 31-37 relates to a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors.

Thus, the object underlying these claims is the provision of a method of treating a neoplastic disease.

The posed solution is a synergistic combination of at least two proteosome

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

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inhibitors.

The application shows a synergistic effect for the combination of salinosporamide A and bortezomib.

However, a synergistic effect cannot be generalized to all possible combinations of at least two proteasome inhibitors.

In conclusion, an inventive step is acknowledged for the subject-matter of claim 37 within the meaning of Article 33(3) PCT.

The subject-matter of claims 31-36 does not involve an inventive step under Article 33(3) PCT.

6. Certain published documents (Rule 70.10)

D4: WO 2005/002572 A (NEREUS PHARMACEUTICALS, INC; PALLADINO, MICHAEL; NEUTEBOOM, SASKIA, TH) 13 January 2005 (2005-01-13)

D5: WILLIAMS PHILIP G ET AL: "New cytotoxic salinosporamides from the marine actinomycete *Salinispora tropica*" JOURNAL OF ORGANIC CHEMISTRY, vol. 70, no. 16, August 2005 (2005-08), pages 6196-6203, XP002376431 ISSN: 0022-3263

D6: MACHERLA VENKAT R ET AL: "Structure-activity relationship studies of salinosporamide a (NPI-0052), a novel marine derived proteasome inhibitor" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 11, June 2005 (2005-06), pages 3684-3687, XP002376432 ISSN: 0022-2623

The above cited documents could become relevant by entering the regional European phase.